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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,098	STROVEL ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-25,28-30,32-34,36,56-58,62,67-72,75,76 and 79-83* is/are pending in the application.

4a) Of the above claim(s) *9-25,28-30,32-34,36,56-58,62,67-72,75,76 and 79-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 28, 2010 has been entered.

Claims 5-25, 28-30, 32-34, 36, 56-58, 62, 67-72, 75-76, and 79-83 are currently pending.

Claims 9-25, 28-30, 32-34, 36, 56-58, 62, 67-72, 75-76, and 79-83 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 24, 2009.

Claims 5-8 have been examined herein.

2. Applicants are reminded that the current status of all of the claims in an application, including any previously canceled or withdrawn claims must be given. In the instant case the status of claims 63-66, 73-74, and 77-78 has not been given. In response to this Office Action Applicants should file a new set of claims which indicate the current status of all of the claims.

Specification

3. The abstract of the disclosure is objected to for exceeding 150 words. Applicants are reminded that the abstract in an application may not exceed 150 words in length. Additionally the abstract is objected to for recited the phrase "said gene" in line 4. Applicants are reminded that the form and legal phraseology often used in patent claims, such as "means" and "said", should be avoided. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112 1st paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection has been modified:

Claims 5-8 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for diagnosing a predisposition to hepatocellular carcinoma in a human patient, comprising: (a) obtaining a liver tissue sample from said human suspected of having hepatocellular carcinoma (b) assaying said liver tissue sample to determine the gene copy number of HSPC150; (c) diagnosing said human patient with a predisposition to hepatocellular carcinoma when the gene copy number of HSPC150 is increased in said liver tissue sample relative to the gene copy number of HSPC150 in a non cancerous liver tissue control sample.

does not reasonably provide enablement for a method for diagnosing any type of cancer or precancerous condition in any type of mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Nature of the Invention

The invention is drawn to a method of diagnosing cancer or a precancerous condition in a mammal. The method comprises (a) obtaining a cell or tissue sample from a mammal suspected of having cancer or a precancerous condition and determining for said sample the gene copy number of the HSPC150 gene (b) comparing said gene copy number of step (a) to the gene copy number of the HSPC150 gene from a sample of a corresponding cell or tissue from a mammal of the same species not having cancer of the type being diagnosed whereby a higher gene copy number determined in step (a) relative to that in step (b) indicates the presence of a cancer or pre-cancerous condition in the mammal of step (a) and results in a diagnosis of cancer or a pre-cancerous condition in said mammal. Thus the nature of the invention requires a reliable association between an increased copy number of the HSPC150 gene and the presence of cancer or a precancerous condition in a mammal. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Scope of the Claims:

The claims encompass a method wherein the cancer or precancerous condition is any type of cancer (breast, colon, cervical, lung, brain etc) or any type of precancerous condition (actinic keratosis, atrophic gastritis, cervical dysplasia etc). Only claim 7 is limited to specific cancers wherein the cancer is selected from the group consisting of breast, colon, lung, prostate, ovarian, pancreatic, cervical, and kidney cancer. Additionally the claims encompass a method for diagnosing cancer or a precancerous condition in any type of mammal (human, cat, whale, bat). Only claim 6 is limited to a specific type of mammal wherein the mammal is a human. Further the claims encompass obtaining a cell or tissue sample wherein the cell or tissue is derived from anywhere (i.e., saliva, hair, breast tissue).

Teachings in the Specification:

The specification teaches that the present invention relates to genes that have been identified as being amplified and/or over expressed, which can include increased copy number thereof, in cancerous cells. The genes have been identified through a combination of CGH, SKY, expression analysis, and reverse transcriptase PCR. The genes are listed in Table 1.

In the instant case the elected gene, HSPC150 protein similar to ubiquitin-conjugating enzyme, is listed in Table 1. Specifically Table provides the following information about HSPC150-- serial no: 119, SEQ ID NO: 107, Accession no: AI990409, tissue: breast, p_m: metastatic, chromosome: 1, band: q32.1, unigene: Hs.5199.

The information present in Table 1 is problematic for several reasons. First of all Table 1 does not indicate if the HSPC150 gene is over expressed, if it has an increased copy number, or both. Here it is important to note that increased expression is not necessarily equivalent to increased copy number. The specification (page 27) even states that if a gene is found to be present in multiple copies it may not be actively being over expressed. Therefore based on the limited information provided in Table 1 the specification does not provide support for the HSPC150 gene having an increased copy number in cancer or pre cancerous conditions. Additionally it is noted that Table 1 teaches that the tissue is breast. Here its unknown if this means that the HSPC150 gene was only associated with breast cancer (opposed to the other types of cancers and pre cancerous conditions encompassed by the claims) or if this means that the HSPC150 gene was only detected is breast tissue samples (opposed to being detected in other types of samples encompassed by the claims). Further its unclear if the genes that were identified as being amplified and/or over expressed, were detected in a representative number of different types of mammals since the claims encompass any mammal.

State of the Art and the Unpredictability of the Art:

As discussed above the specification does not provide support for the HSPC150 gene having an increased copy number in any type of cancer or any type of precancerous condition since Table 1 does not indicate if the HSPC150 gene was over expressed, if it had an increased copy number, or both. It is noted that the instant specification (page 27) even states that if a gene is found to be present in multiple

copies it may not be actively being over expressed. For this reason a finding that the HSPC150 is over expressed in a particular type of cancer or pre cancerous condition would not necessarily mean that the HSPC150 has an increased copy number in that particular type of cancer or precancerous condition. If possible applicants should clarify if the HSPC150 gene actually had an increased copy number, if it was over expressed, or both.

The prior art Crawley (Genome Biology 2002 Vol 3 No 12) identified frequent cytogenic aberration in hepatocellular carcinoma (abstract). Crawley teaches a list of genes whose expression changed at least twofold in 70% of tumor samples in the same relative direction as the cytogenic change and are located in regions identified as cytogentically abnormal by CGMA in at least 35% of samples (Table 2). Relevant to the instant claims the HSPC150 gene is listed in Table 2. There was a 5.6 fold difference in tumor tissue gene expression relative to non cancerous tissue for the HSPC150 gene located at Iq:209. As such the prior art of Crawley provides support for a method for diagnosing a predisposition to hepatocellular carcinoma in a human patient, comprising: (a) obtaining a liver tissue sample from said human suspected of having hepatocellular carcinoma (b) assaying said liver tissue sample to determine the gene copy number of HSPC150; (c) diagnosing said human patient with a predisposition to hepatocellular carcinoma when the gene copy number of HSPC150 is increased in said liver tissue sample relative to the gene copy number of HSPC150 in a non cancerous liver tissue control sample.

Even though there is evidence in the prior art that the HSPC150 gene has an

increased copy number in hepatocellular carcinoma it is highly unpredictable as to whether the results obtained with hepatocellular carcinoma could be extrapolated to other cancers and pre cancerous conditions. For example Adnane (Oncogene 1991 Vol 6 pages 659-663) teaches that the analysis of 387 human breast tumor DNAs revealed that BEK (also called FGFR2) was amplified in about 12% of the cases (page 659, col 2). On the other hand Sasaki (Brain Tumor Pathology 2003 Vol 20 pages 59-63) teaches a genome microarray spotted with 287 target genes was used to analyze resected tissue from 11 different high grade gliomas. A high frequency of deleted genes was observed in 6 of 11 cases (54.5%), including FGFR2 (abstract). These papers are relevant to the present situation because they support the argument that it is highly unpredictable as to whether the amplification of HSPC150 in hepatocellular carcinoma could be extrapolated to other cancers and precancerous conditions.

Further even though there is evidence in the prior art that the HSPC150 gene has an increased copy number in humans with hepatocellular carcinoma it is highly unpredictable as to whether the results obtained with humans could be extrapolated to other mammals. Knowledge that a particular gene such as HSPC150 is amplified in one organism (i.e. humans) with hepatocellular carcinoma does not allow one to conclude that this gene will also be amplified in other organisms with hepatocellular carcinoma.

Quantity of Experimentation:

In the instant case there is no evidence in the specification that increased copy number of HSPC150 is actually associated with cancer or precancerous conditions. For this reason one would have to conduct extensive experimentation. For example,

such experimentation may involve using probes specific for HSPC150 gene to detect the copy number of the HSPC150 gene in large number of samples obtained from all different types of mammals with all different types of cancer and precancerous conditions. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response To Arguments Regarding Enablement

5. In the response filed September 28, 2010, the Applicants traversed the enablement rejection.

In the response (page 2) the Applicants state that they appreciate and thank the Examiner for indicating that identifying a cancerous cell of the breast or the detection of breast cancer is enabled subject matter.

These remarks have been fully considered but it is noted for the record that the examiner has never indicated that the specification was enabled for breast cancer (see Office Actions of November 9, 2009 and March 31, 2010). In fact the Examiner argues

that Table 1 does not indicate if the HSPC150 gene is over expressed, if it has an increased copy number, or both.

In the response (pages 2-3) the Applicants state that the Examiner relies on Knuutila et al. (American Journal of Pathology, 1998, vol. 152, no. 5, pages 1107-1123) to support her argument that it is unpredictable as to whether a cancer gene marker found in single type of cancer could be used for determining the presence of other types of cancers.

These remarks have been fully considered but it is noted for the record that the examiner has never cited Knuutila et al (see Office Actions of November 9, 2009 and March 31, 2010). However the previous Office Actions do address the fact that even if the HSPC150 gene was found to have an increased copy number in one type of cancer it is highly unpredictable as to whether the results obtained could be extrapolated to other cancers and pre cancerous conditions. The Examiner cited Adnane (Oncogene 1991 Vol 6 pages 659-663) and Sasaki (Brain Tumor Pathology 2003 Vol 20 pages 59-63) for support. While Adnane teaches that BEK (also called FGFR2) is amplified in breast cancer, Sasaki teaches that FGFR2 is deleted in high grade gliomas. These papers are relevant to the present situation because they support the argument that it is highly unpredictable as to whether the amplification of HSPC150 in one type of cancer could be extrapolated to other cancers and precancerous conditions.

In the response (page 4) the Applicants assert that once in possession of the instant specification, one of ordinary skill in the art would have been able to practice the instant claims without undue experimentation, because the HSPC150 expression is

evident in cells other than breast cancer which make it a useful tool for the identification of chromosomal abnormalities. Applicants state that one of ordinary skill in the art would have conveniently been able to practice the claimed invention.

This argument has been fully considered but is not persuasive. In the instant case the intended use of the claimed method is to diagnose cancer or a pre cancerous condition in a mammal. The claimed invention requires a reliable association between an increased copy number of the HSPC150 gene and the presence of cancer or a precancerous condition. The fact that HSPC150 expression is evident in cells other than breast cancer is not relevant because the claims require determining gene copy number rather than gene expression. While differential expression of a gene can be effected by a difference in gene copy number, it is not the only mechanism of increasing gene expression. Therefore enablement is not based on the fact that HSPC150 is expressed in other cells, but whether the gene is amplified in samples of other types of cancer and whether the amplification is correlated with the presence of different types of cancer.

In the response (page 4) the Applicants state that the claims are directed to a method of detecting cancer by measuring HSPC150 expression. The Applicants assert that there is no requirement for a Patentee to describe all possible cell types for diagnosis of cancer where the specification and the prior art sufficiently enable one of skill in the art to make and use the invention.

These arguments have been fully considered but are not persuasive. The claims are not drawn to a method of detecting cancer by measuring HSPC150 expression; rather the claims require determining the copy number of HSPC150 in a sample. This is

not equivalent to measuring expression. The examiner agrees that there is no requirement for a Patentee to describe all possible cell types for diagnosis of cancer however since the Applicants are claiming the genus of cancer they must show that the association works in a representative number of different cancers. In the instant case this has not been done. Further it is noted that the examiner cited Adnane (Oncogene 1991 Vol 6 pages 659-663) and Sasaki (Brain Tumor Pathology 2003 Vol 20 pages 59-63) because Adnane teaches that BEK (also called FGFR2) is amplified in breast cancer, while Sasaki teaches that FGFR2 is deleted in high grade gliomas. These papers are relevant to the present situation because they support the argument that it is highly unpredictable as to whether the amplification of HSPC150 in one type of cancer could be extrapolated to other cancers and precancerous conditions. Applicants have not produced evidence to the contrary regarding this argument.

In the response (pages 4-5) the Applicants state that the nature of the invention relates to diagnostic methods for cancer by detecting increased expression of the marker HSPC150. They argue that the specification provides ample background description about HSPC150 expression in cancer cells and, in some examples, the related co- expression of cell cycle and regulatory markers in the specification.

These arguments have been fully considered but are not persuasive. As stated above the claims are not drawn to a method of detecting cancer by measuring HSPC150 expression, rather the claims require determining the copy number of HSPC150 in a sample.

In the response (pages 5-6) the Applicants argue that the expression of various markers as a means of detecting cancer cells are known in the art. Applicant's respectfully request the Examiner consider HSPC150 as a tool to view the abnormalities associated more broadly with cancers. They argue that the present invention seeks to use HSPC150 as a visualization tool for more broadly measuring cancer abnormalities at the chromosomal level, rather than morphological level or even the molecular level.

These arguments have been fully considered but are not persuasive. The fact that it was known in the prior art that altered gene expression can be used as a marker for cancer is irrelevant because the claims do not require determining if gene expression is increased, rather they require determining if copy number is increased. It has been clearly conveyed to Applicants that it is highly unpredictable as to whether the findings in the prior art that the HSPC150 gene has an increased copy number in hepatocellular carcinoma could be extrapolated to other cancers and pre cancerous conditions. In view of the teachings of Adnane (Oncogene 1991 Vol 6 pages 659-663) and Sasaki (Brain Tumor Pathology 2003 Vol 20 pages 59-63) the fact is plain and clear that a particular gene will not be amplified in all types of cancer.

In the response (pages 5-6) the Applicants cite PG Pub 2007/0059697, filed by the same inventive entity. The Applicants refer to Table 1 of the publication and assert that increased copy number correlates to various types of cancer. They state that SEQ ID NOs: 26, 356, 579, 721, 722, 833, 834, 855, 856 are all on the same chromosomal region as HSPC150 and are shown to be implicated with various types of cancer such as breast, colon, lung, and prostate.

These arguments have been fully considered but are not persuasive. The fact that all these different sequence found on the similar area of the chromosome demonstrates the fact that not all genes are implicated with the same types of cancers. If it were so, all of these SEQ ID NOs should have been correlated with the same types of cancer.

In the response (page 7) the Applicants contend that there is ample information in the art about HSPC150, gene markers co-expressed with HSPC 150 and cancer diagnostics. They argue that consistent with the state of law, there is no need for the applicant to articulate material already known in the art. Applicant submit that the teachings of the specification are sufficient for those of ordinary skill in the art who would have been interested in identifying various cancer cell types using HSPC 150 as a marker.

These arguments have been fully considered but are not persuasive. The nature of the invention requires a reliable association between an increased copy number of the HSPC150 gene and the presence of cancer or a precancerous condition in a mammal. The question is not whether HSPC150 was known in the art but whether or not HSPC150 will be amplified in different types of cancer. As stated previously it is unpredictable as to whether it is possible to extrapolate the finding that the HSPC150 gene has an increased copy number in hepatocellular carcinoma to other cancers and pre cancerous conditions.

In the response (pages 7-8) the Applicants state that the specification discloses that HSPC150 expression can be used as a diagnostic marker for breast, colon, lung,

and prostate malignancies. They state that examples show that several genes were found to be co expressed with high levels of HSPC150.

These arguments have been fully considered but are not persuasive. Again the claims do not require determining the expression level of HSPC150. The claims require determining the copy number of HSPC150. Expression level and copy number are distinctly different from one another. Applicants have not provided any evidence that in breast, colon, lung and prostate cancer the HSPC150 gene has an increased copy number.

In the response (page 9) the Applicants argue that the rejection should be withdrawn because the quality of experimentation needed would have been routine where the skills of those of skill in the art is high and where such unpredictability in the art is low given the disclosure of the specification and the knowledge set forth in the prior art.

This argument is not persuasive. As stated previously it is unpredictable as to whether it is possible to extrapolate the finding that the HSPC150 gene has an increased copy number in hepatocellular carcinoma to other cancers and pre cancerous conditions. The examiner has even cited two references to support this argument (Adnane and Sasaki). Because there is no evidence in the specification that increased copy number of HSPC150 is associated with a representative number of different cancer or precancerous conditions additional experimentation is required. One would have to perform extensive experimentation using probes specific for HSPC150 gene to detect the copy number of the HSPC150 gene in large number of samples obtained

from all different types of mammals with all different types of cancer and precancerous conditions. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

In the response (pages 9-10) the Applicants state that the Examiner has failed to show, the unpredictability of the art for correlating increased chromosomal aneuploidy, measured by HSPC150, to cancer. They state that the Examiner agrees that with respect to breast cancer cells this correlation is predictable. Since cancer is a genetic disease and other markers known to on the same chromosome region as HSPC 150 are associated with various cancers, HSPC150 as a probe target to measure aneuploidy in cells would be predictable in view of the art and the disclosure herein.

These remarks have been fully considered but are not persuasive. The examiner has not failed to show the unpredictability in the art. The examiner has even cited two references to support her argument (Adnane and Sasaki). It is also noted that the examiner has never stated that the correlation with breast cancer is predictable. The specification (page 6) states that the present invention relates to a set of genes that are amplified and/or over expressed genes in cancer cell lines and have been localized to various chromosomal regions of interest. Particurarly the examiner argues that it is not clear from Table 1 if the HSPC150 gene is over expressed, if it has an increased copy number, or both. Based on the limited information provided in Table 1 the specification does not provide support for the HSPC150 gene having an increased copy number in cancer or pre cancerous conditions. Even if the specification did teach a reliable and robust correlation between increased copy number of HSPC150 and breast cancer it

would be highly unpredictable if there would also be a reliable and robust correlation between increased copy number of HSPC150 and the other types of cancers that are encompassed by the claims. The specification does not provide any evidence that other cancers will also have an increased copy number of HSPC150. Further since the claims encompass any mammals it is relevant to point out that the Applicants have not provided any evidence that the HSPC150 gene has an increased copy number in a representative number of different mammals. Since these issues have not been clarified the Examiner maintains the position that undue experimentation would be required to make and/or use the claimed invention.

6. It is noted that claims rejected in this portion of the Office Action under 35 USC 103 as being obvious over, the prior art have been previously rejected in this Office Action under 35 USC 112 1st paragraph as not fully enabled by the specification as originally filed. In the instant case, where the prior art does render obvious particular embodiments of the broadly claimed methods, the prior art is not sufficient to enable the skilled artisan to practice the claimed method in the full scope of the claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a new ground of rejection:

8. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crawley (Genome Biology 2002 Vol 3 No 12 pages 1-8 published online 11/25/2002).

Regarding Claim 5 Crawley teaches obtaining liver samples from human patients with hepatocellular carcinoma (HCC) and corresponding non cancerous liver samples. Crawley teaches determining the level of HSPC150 gene expression in the samples. Crawley teaches that HSPC150 gene had a 5.6 fold difference in tumor tissue gene expression relative to non cancerous tissue (abstract, page 7, col 1-2, and Table 2).

Regarding Claim 6 Crawley teaches a method wherein the samples were obtained from a human (page 7, col 1).

Crawley does not teach determining the copy number of the HSPC150 gene in the samples (clm 5).

However Crawley teaches that using comparative genomic microarray analysis CGMA is it possible to predict chromosomal amplifications and deletions by organizing gene expression data by genomic mapping location and scanning for regions that contain a statistically significant number of gene expression values that change in the same relative direction (abstract, page 2, col 1). Crawley teaches that they applied CGMA analysis to a large HCC microarray dataset to demonstrate its validity as an alternative to CGH and to identify candidate genes in regions of frequent cytogenic change. Crawley teaches that using CGMA they identified 13 regions of cytogenic change in the HCC samples, including +1q which is the region where the HSPC150 gene is located. (abstract, page 2 col 2, and Table 2). As such Crawley predicts that the HSPC150 gene is amplified (i.e. has an increased copy number) in HCC samples relative non cancerous samples.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Crawley by detecting the copy number of the HSPC150 gene in the samples. Crawley teaches that although techniques such as comparative genomic hybridization have traditionally been used to identify cytogenic aberrations, it might also be possible to identify them indirectly from gene expression studies. Crawley teaches CGMA predicts regions of cytogenic change by searching for regional gene expression biases. Based on the teachings in Crawley one of skill in the art would have been motivated to detect the copy number of the HSPC150 gene in the samples using a technique such as CGH in order to confirm the results found using the CGMA assay and to determine if CGMA is an accurate predictor

of chromosomal imbalance. Because Crawley predicts that the HSPC150 gene is amplified (i.e. has an increased copy number) in HCC samples relative non cancerous samples a method for diagnosing hepatocellular cancer by detecting an increased copy number of HSPC150 relative to non cancerous cells would have been obvious to one of skill in the art at the time of the invention.

The following is a new ground of rejection:

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Crawley (Genome Biology 2002 Vol 3 No 12 pages 1-8 published online 11/25/2002) in view of GenBank (Accession No AI990409 GI 5837290 entered 9/7/1999).

Regarding Claim 8 Crawley does not teach a method wherein the HSPC150 gene encodes the same gene product as the polynucleotide of SEQ ID NO: 107.

However GenBank teaches a nucleic acid sequence that is 100% identical to SEQ ID NO 107. (QY=SEQ ID NO: 1, Db=GenBank sequence).

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Qy          1 CAACATTAAATGACTATTTATTTTTCAGGTTTAAAAGATTTCAAAATACATATGTACAAG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 CAACATTAAATGACTATTTATTTTTCAGGTTTAAAAGATTTCAAAATACATATGTACAAG 60

Qy         61 ATAAATAAACTACACAAAAATTATGTCATCAAATATATTTAAAAAAAAATTCAAGGTAGG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 ATAAATAAACTACACAAAAATTATGTCATCAAATATATTTAAAAAAAAATTCAAGGTAGG 120

Qy        121 CAACTTAGATCACCTTGGCAAAGAACACATTAACTAAGATGAACCAGGACAAGTCCCCTA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 CAACTTAGATCACCTTGGCAAAGAACACATTAACTAAGATGAACCAGGACAAGTCCCCTA 180

Qy        181 AACATCAGGATGAAATTTCTTTTCTATGCCTACTAGCTGACTGGCCTTCCTTTTCTGTGT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 AACATCAGGATGAAATTTCTTTTCTATGCCTACTAGCTGACTGGCCTTCCTTTTCTGTGT 240

Qy        241 TGAGTTGTGTACTCTGGAGTCACCAGCCTCTGGTAGATTATCAAGCATCTCTTCCTCATC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 TGAGTTGTGTACTCTGGAGTCACCAGCCTCTGGTAGATTATCAAGCATCTCTTCCTCATC 300

Qy        301 AGCCTTTTGTTTCTGTCTTGCATGCTTCTCTGTCCACTGTCTGGCATTCTTGAGGAAGGC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 AGCCTTTTGTTTCTGTCTTGCATGCTTCTCTGTCCACTGTCTGGCATTCTTGAGGAAGGC 360

Qy        361 TGGCTTATTATATTTAAATTCTGAGGATATGTCAGCCATGAGCGGGTCATCAGGGTTGGG 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 TGGCTTATTATATTTAAATTCTGAGGATATGTCAGCCATGAGCGGGTCATCAGGGTTGGG 420

Qy        421 TTCTGACATGAGCAGCTGAATAGAGGTCAACACAGTTGCGATGTTGAGGGATGGTCTCCA 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 TTCTGACATGAGCAGCTGAATAGAGGTCAACACAGTTGCGATGTTGAGGGATGGTCTCCA 480
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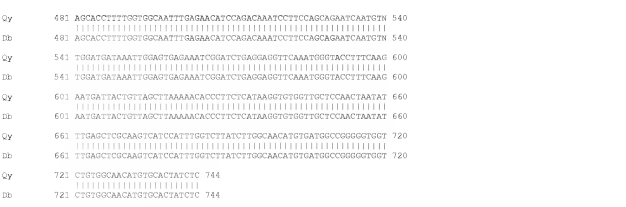

Since these sequences are 100% identical it is a property of the GenBank sequence that it encodes the same gene product as SEQ ID NO: 7.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Crawley by detecting the copy number of a gene that encodes the same gene product as the polynucleotide of SEQ ID NO: 107. In the instant case GenBank teaches a nucleotide sequence that is 100% identical to SEQ ID NO: 107 and therefore encodes the same gene product as SEQ ID NO: 107. Because Crawly predicts that the HSPC150 gene is amplified in HCC one of skill in the art would have been motivated to detect the copy number of the GenBank sequence that encodes the same gene product as the polynucleotide of SEQ ID NO: 107 for the benefit of being able to determine the copy number of the HSPC150 gene.

Conclusion

10. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571)

272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Amanda Shaw/
Examiner 1634